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Liver Transplantation for Recurrent Hepatocellular Carcinoma on Cirrhosis After Liver Resection: University of Bologna Experience

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Liver resection (LR) for patients with small hepatocellular carcinoma (HCC) with preserved liver function, employing liver transplantation (LT) as a salvage procedure (SLT) in the event of HCC recurrence, is a debated strategy.

From 1996 to 2005, we treated 227 cirrhotic patients with HCC transplantable: 80 LRs and 147 LTs of 293 listed for transplantation. Among 80 patients eligible for transplantation who underwent LR, 39 (49%) developed HCC recurrence and 12/39 (31%) of these patients presented HCC recurrence outside Milan criteria. Only 10 of the 39 patients underwent LT, a transplantation rate of 26% of patients with HCC recurrence.

According to intention-to-treat analysis of transplantable HCC patients who underwent LR (n = 80), compared to all those listed for transplantation (n = 293), 5-year overall survival was 66% in the LR group versus 58% in patients listed for LT, respectively (p = NS); 5-year disease-free survival was 41% in the LR group versus 54% in patients listed for LT (p = NS).

Comparable 5-year overall (62% vs. 73%, p = NS) and disease-free (48% vs. 71%, p = NS) survival rates were obtained for SLT and primary LT for HCC, respectively.

LR is a valid treatment for small HCC and in the event of recurrence, SLT is a safe and effective procedure.

Key words: Disease-free survival, operative mortality, outcome, partial hepatectomy, salvage transplantation

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and its incidence will increase in the next two decades both in Europe and the United States (1,2). HCC now constitutes the most frequent cause of death in cirrhotic patients (3). Strict follow-up programs in cirrhotic patients allow identification of HCC at an early stage when curative nontransplant treatments are possible (4).

Liver resection (LR) is the first-line treatment in patients with HCC and preserved liver function (Child class A) (5) with acceptable results in terms of perioperative risk (6) and overall survival (7); it is, however, linked to a high incidence of HCC recurrence, up to 50–70% of cases at 5 years of follow-up (8–10). Liver transplantation (LT) is advisable in patients with HCC and decompensated cirrhosis (Child class B-C) (5) with excellent results in term of overall and disease-free survival in selected patients (11). Recently, promising results after LT have been reported also with extension of the Milan criteria (12). The main problem affecting the applicability of the LT option is the high dropout rate from the waiting list related to HCC progression (13,14), despite the systematic use of nonsurgical bridging techniques such as trans-arterial chemoembolization (TACE) (15) and/or radio-frequency ablation (RFA) (16) or percutaneous alcohol injection (PEI) (17), caused by organ shortage in relation to the continuously increasing number of patients awaiting LT (18). Supported by good results in terms of overall survival from LR for HCC in selected transplantable patients with preserved liver function and working with the assumption that at the time of HCC recurrence LT can be performed secondarily, a third surgical strategy named 'salvage transplantation' was first proposed by Majno et al. (19) with encouraging results.

Materials and Methods

From January 1996 to November 2005, 317 consecutive patients with documented HCC, by two imaging studies, were treated by hepatic resection (n = 170) or LT (n = 147) at our institution.

Thirty-six patients (5 LR patients and 31 LT patients) included in the analysis had two imaging studies documenting HCC; they were treated with preoperative ablative therapies and complete tumor necrosis was found on the operative specimen, preventing pathological confirmation of HCC.

The 170 cirrhotic patients treated by liver resection during the study period were selected mainly when they had one or two nodules, preserved hepatic function (Child-Pugh A) and pre- and intra-operative absence of macroscopic portal invasion and of an extrahepatic tumor. All resections were potentially curative. Among this group, 90 patients (53%) were considered as non-transplantable because of age >65 years (n = 70), maximum tumor size exceeding 5 cm (n = 11) or large and multinodular (up to three nodules and >3 cm; n = 9) according to the selection criteria used for transplantation in the same period. The remaining 80 patients (47%) were potentially transplantable but were treated by liver resection since this was the primary preference to LT, because of organ shortage. Postoperative follow-up included liver function tests, dosage of serum alpha-feto protein (AFP) and abdominal ultrasonography on a 3-month basis in the first 6 months after surgery and on a 6-month basis in the subsequent period, and chest-abdominal CT scan once a year. The policy was to consider LT for patients who would have developed hepatic HCC recurrence, documented by liver ultrasonography and confirmed by CT scan of the abdomen, or deterioration of liver function after resection. Accordingly, among the 80 transplantable patients, 16 (20%) were subsequently transplanted: 10 (12.5%) for tumor recurrence and 6 (7.5%) for hepatic decompensation.

The 147 patients transplanted for HCC in the study period were selected according to the following pretransplant criteria: age <65 years, absence of metastatic lymph nodes or extrahepatic spread at the preoperative evaluation, absence of macroscopic vascular invasion, no history of other malignant tumors within the last 5 years, HCC meeting Milan criteria. As a result, the study population consisted of 80 LR transplantable patients and 147 LTs out of 293 listed patients in the study period. The indication for LT depended mainly on the technical un-resectability of the HCC or on decompensated liver function (Child-Pugh class B or C).

Preoperative staging routinely included hepatic ultrasound, chest and abdominal CT, and bone scintigraphy to look for any extrahepatic tumor spread.

Patients with HCC were given no priority on the waiting list as compared with other patients from 1996 to 2003 when recipients were selected for LT according to their Child score and HCC patients were eligible for marginal donors (20); after April 2003 our local policy led to adopting the model for end-stage disease (MELD) score (21) for LT candidates.

Patients with HCC listed in our institution did not receive a MELD score upgrade, similar to US policy, but the score was calculated by considering their real MELD score, the waiting time with tumor and the tumor stage. In particular, in the first period of MELD experience, the MELD score for HCC patients was calculated in the following way: real MELD score + 5 points for T1, 8 points for T2 + 1 point for every month on the waiting list with a diagnosis of HCC. As a result, we observed a high rate of LT for HCC (22); on the basis of these data, the points added to the HCC patients scores were reduced as following: real MELD score + 3 points for T1 or 6 for T2 + 0.5 for T1 or 1 for T2 every month on the waiting list with a diagnosis of HCC.

Tumor-stage T1 was a single HCC with a diameter ≤3 cm, while T2 was a single HCC with a diameter between 3 and 5 cm or multiple HCCs no more than three with a diameter ≤3 cm.

This ranking for HCC patients led to a rate of removals from the list similar to the non-HCC patients (22). The survival data were not affected by changes in allocation policy: 3-year overall survival was 83% in patients transplanted before 2002, 74% in patients transplanted adopting MELD score and 70% in patients transplanted adopting the MELD-modified score.

The minimum criteria for placing adults on the liver transplant waiting list were those reported by the American Society of Transplant Physicians and the American Association for Study of Liver Disease (23) in both eras. To avoid patient dropout from the waiting list in the LT group and tumor growth in the LR group, and to achieve a good degree of necrosis of the tumor, TACE is performed whenever possible. RFA or PEI are applied if the HCC is <3 cm in size and not more than three nodules are present, not in contiguity with vascular or biliary structures and easy to reach by the transabdominal approach with abdominal ultrasonography guide and not deep in the liver parenchyma. In particular, a complete degree of tumor necrosis was achieved in 31 cases out of 68 (45%) in the LT group (22 with TACE, 3 with a combination TACE and RFA, 5 with RFA and 1 with PEI) and in 5 cases out of 31 (16%) in the LR transplantable group (all with TACE).

Design of the study

Liver resection in patients potentially eligible for transplantation (n = 80) was compared with primary LT patients (n = 147), to assess the outcome of each treatment strategy. Survival in each group was calculated from the time of the primary procedure (LR or LT). Patients with salvage LT were included in the resection group, and their survival was calculated from the time of the resection. Disease-free survival was computed considering patients that developed HCC recurrence and patients who died as censored.

An intention-to-treat analysis was performed of all transplantable HCC patients who underwent resection (n = 80) compared to all those listed for transplantation in the study period, including only those that were within Milan criteria (n = 293), as well as considering the patients aged below 65 years in each group (Table 1). As a consequence, intention-to-treat analysis started at the time of listing for liver transplantation for those who were considered for transplantation and at the time of resection for those who underwent resection; assuming the time between the decision to resect and actually resecting was short (<21 days). Disease-free survival was computed considering patients that developed HCC recurrence after LT or LR and patients who died as censored and in the group of patients listed for LT also patients who died on the waiting list or patients who were excluded from the waiting list for any reasons.

Salvage LT after LR for HCC (n = 16) was compared to primary LT for HCC (n = 147) to assess the operative risk and the postoperative complications

Table 1: Indications for patients listed for LT and LR potentially transplantable patients

Indications	Patients listed for LT (n = 293)	LR potentially transplantable (n = 80)
Age	<= 65 years	<= 65 years
Child A	Yes	Yes
Child B	Yes	Yes
Child C	Yes	No
Gastroesophageal varices	Yes	No
Ascites	Yes	No
Encephalopathy	Yes	No
MELD score	>= 13	<= 11
HCC features:		
- Number of nodules	< = 3	<= 3
- Maximum size of the lesions (cm)		
- Solitary HCC	<= 5 cm	<= 5 cm
- Multinodular HCCs	<= 3 cm each	<= 3 cm each

LT = liver transplantation; LR = liver resection; MELD = model for end-stage disease; HCC = hepatocellular carcinoma.

of this surgical procedure. Survival in each group was calculated from the time of transplantation.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS 10.0., Inc., Chicago, IL). Parametric analyses were performed using one-way analysis of variance (ANOVA); nonparametric analyses were performed using the chi-square test or Fisher exact test as appropriate. Survival curves were generated using the Kaplan-Meier method, with differences between curves assessed using the log-rank test. Possible risk factors for HCC recurrence were analyzed by univariate and multivariate analysis. Stepwise logistic analysis was used to test for independent significance of variables that were statistically significant by univariate tests. Results were reported as the mean ± standard error of the mean, and significance levels were set at $p < 0.05$.

Results

LR in patients potentially transplantable versus primary LT

In the resection group, patients were older (59 ± 6 vs. 55 ± 7, $p < 0.0001$), with a greater prevalence of virus C-related cirrhosis (76% vs. 54%, $p = 0.003$) and Child A status (82% vs. 4%, $p < 0.0001$), compared with the LT group. Preoperative tumor characteristics showed that maximum size >30 mm was more frequent in the LR group (32% vs. 9%, $p < 0.0001$) and serum levels of AFP were higher in the LR group compared to the primary LT group (220 ± 808 vs. 42 ± 97 ng/mL, $p = 0.01$). Preoperative nonsurgical treatments (TACE, RFA, PEI) were more prevalent in the primary LT group (46% vs.39%, p = NS) (Table 2).

Table 2: Patient and tumor characteristics in primary LT and LR potentially transplantable group

Variables	Primary LT (n = 147)	LR potentially transplantable (n = 80)	p
Gender M/F	126 (86%)/ 21 (14%)	63 (79%)/ 17 (21%)	NS
Recipient age	55 ± 7	59 ± 6	<0.001
Cirrhosis etiology:			
Alcohol	21 (14%)	8 (10%)	
HCV+	79 (54%)	61 (76%)	0.003
HBV+	43 (29%)	9 (11%)	
HCV+/HBV+	4 (3%)	2 (3%)	
Child A	6 (4%)	66 (82%)	< 0.001
Child B	53 (36%)	14 (18%)	
Child C	88 (60%)	–	
MELD	17.8 ± 10.7	8.56 ± 1.31	<0.001
Tumor characteristics before LT			
Max size (mm.)	12.7 ± 13.4	31.3 ± 10.3	<0.001
>30 mm	13 (9%)	26 (32%)	<0.001
Mean no of nodules	1.7 ± 1.2	1.11 ± 0.39	<0.001
AFP (ng/mL)	42 ± 97	220 ± 808	0.01
Pre-LT treatments:			
TACE	55 (37%)	28 (35%)	
Alcohol injection	3 (2%)	3 (4%)	
RFA	10 (7%)	–	
All treatments	68 (46%)	31 (39%)	NS

LT = liver transplantation; LR = liver resection; MELD = model for end-stage disease; HCC = hepatocellular carcinoma; AFP = alpha-feto protein; RFA = radio-frequency ablation; TACE = trans-arterial chemoembolisation.

The hospital readmissions rates were: 23 (15.5%) in the LT group versus 6 (7.5%) in the LR group, p = NS.

The initial transplantability of the resected population in relation to preoperative tumor characteristics was 47% (80 of 170). As 16 patients were subsequently transplanted for tumor recurrence or hepatic decompensation, the transplantation rate was 20% (16 of 80).

HCC Recurrence in LR Transplantable Group

Among 80 patients eligible for transplantation that underwent liver resection, 39/80 (49%) developed hepatocellular carcinoma (HCC) recurrence and 12/39 (31%) of this subgroup of patients presented an HCC recurrence outside Milan criteria and only 4/12 (33%) of these are alive.

Among 39 (49%) patients that developed HCC recurrence after liver resection, 27 (69%) patients presented HCC recurrence within Milan criteria and for this reason were theoretically eligible for transplantation. Only 10 of these (37%) were submitted to liver transplantation determining a real transplantability rate of 26% of patients with HCC recurrence and 7 (70%) of these are alive. The remaining 17 patients with HCC recurrence within Milan criteria were not transplanted for the following reasons: in 6 cases (35%) because they were over 65 years at the time of HCC recurrence and 3 (50%) of these are alive, in 3 cases (17%) due to death on the waiting list, in 4 cases (23%) they were still on the waiting list for transplantation, in 1 case (5.8%) for *de novo* uro-genital cancer after liver resection with subsequent death, in 2 case (12%) a re-resection was performed without HCC recurrence at the time of writing and in 1 case (5.8%) due to patient refusal with subsequent death. The site of recurrence was always intrahepatic with only one case of right adrenal gland with HCC recurrence. The mean time to recurrence was 21.8 months ± 20.6 months and in particular the time to recurrence of 90% of the LR patients was 57 months. In particular, we noted no difference in term of time to recurrence, on the remnant liver after LR, in patients with HCC recurrence outside Milan criteria (18.5 months ± 24 months) versus patients with recurrence within Milan criteria (23.4 months ± 19 months, p = NS).

Univariate and multivariate analysis of factors associated with HCC recurrence in LR transplantable patients

We considered the following variables and their relationship with development of HCC recurrence in the

analysis: age of patients >60 years was associated with incidence of HCC recurrence (43% vs. 45% in patients aged <60 yrs), sex of patients (65% vs. 45%, p = 0.04 in females and males, respectively), single versus multiple nodules (45% vs. 50%), nodule size >3 cm (54% vs. 46% in patients with nodules <3 cm), AFP serum levels >20 ng/mL (44% vs. 42% in patients with AFP <20 ng/mL), presence of microvascular invasion on the pathological specimen (54% vs. 46% in patients without microvascular invasion), satellite nodules (54% vs. 46%, in patients with satellite nodules and without satellite nodules, respectively) and tumor grading (56% vs. 48%, in G3-G4 and G1-G2, respectively).

The only variable that proved to be predictive of tumor recurrence at the univariate analysis was female gender against male gender. At the multivariate analysis, the relative risk of HCC recurrence related to female gender was 1.9 (0.9–3.6) with 95% CI: 0.92–3.65, (p = 0.02).

Causes and time of death in primary LT group versus LR transplantable group

Among the 147 patients that underwent transplantation, 30 (20%) died: 7 due to HCC recurrence, 5 due to liver decompensation secondary to HCV recurrence, 5 due to multiorgan failure, 4 due to sepsis, 3 due to other causes, 2 due to liver failure, 1 due to cardiovascular disease, 1 due to intraoperative complication caused by massive bleeding, 1 due to *de novo* tumor and 1 due to HBV recurrence. Among the 80 patients submitted to resection, 34 (42%) died: 18 due to HCC recurrence, 11 due to liver failure, 3 due to HCV recurrence, 1 due to cardiovascular disease and 1 due to *de novo* tumor. Time of death was 37 months ± 32 months in the resection group versus 18 months ± 23 months in the transplantation group, p = 0.007.

Outcome of LR transplantable patients versus primary LT patients

Transplantable resected patients (n = 80) had a similar 5-year overall survival comparable with primarily transplanted patients (n = 147) (66% vs. 73%, p = NS) (Figure 1A). However, transplantable resected patients had a lower 5-year disease-free survival than in primarily transplanted patients (41% vs. 71%, p = 0.001) (Figure 1B). No difference was observed in terms of mean time to recurrence considering both groups of patients: 23 months ± 21 months in the LR group versus 15 months ± 15 months in the LT group, p = NS.

Intention- to-treat analysis of patients listed for LT versus LR transplantable patients

According to the intention-to-treat analysis of all transplantable HCC patients who underwent resection (n = 80) compared to all those listed for transplantation that met Milan criteria (n = 293), the 5-year overall survival was 66% in the LR group versus 58% in patients listed for transplantation, respectively, p = NS (Figure 2A). In particular, considering the 293 patients listed for transplantation, 147 (50%) patients were actually treated with LT and the outcomes of the remaining patients are shown in Table 3.

Following the intention-to-treat analysis principle, the 5-year disease-free survival was 41% in the LR group versus 54% in patients listed for transplantation, respectively, p = NS (Figure 2B).

Safety of salvage LT

Operative mortality was 0% versus 5% in the salvage and primary LT groups, respectively (p = NS). Among the 8 patients who died in the primary LT group: 1 died of intraoperative bleeding, 1 from primary dysfunction complicated

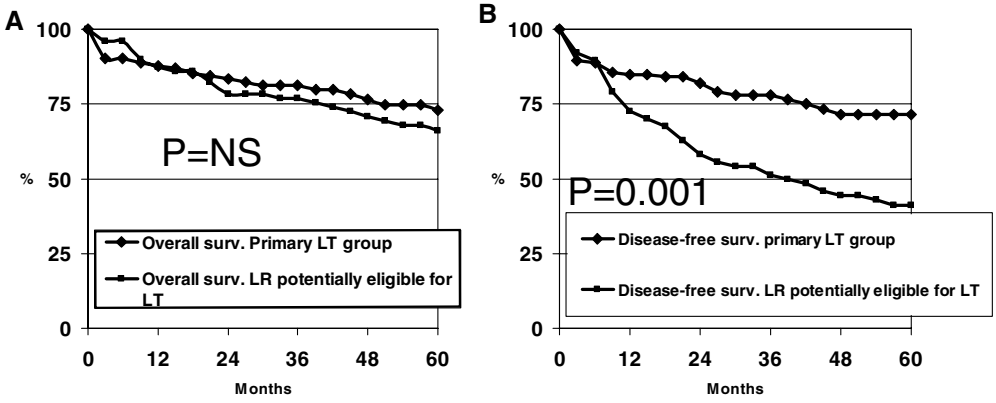

Figure 1: (A) Overall survival after primary LT (n = 147) versus LR in patients potentially eligible for LT (n = 80); (B) Disease-free survival after primary LT (n = 147) versus LR in patients potentially eligible for LT (n = 80).

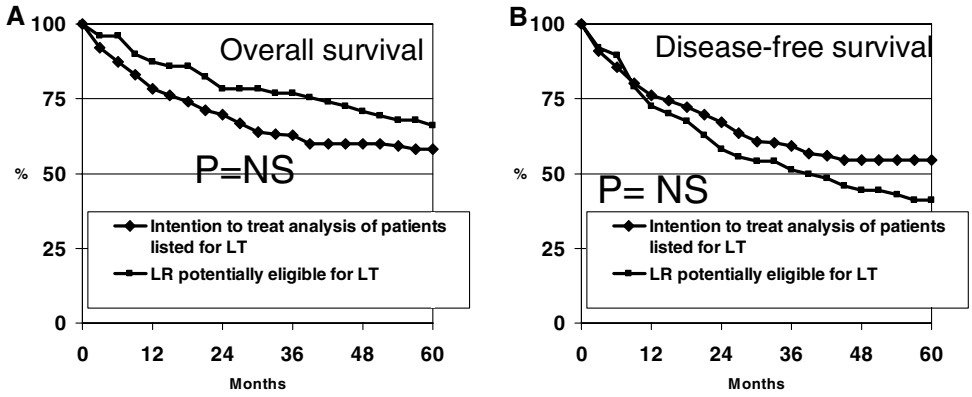

Figure 2: (A) Intention-to-treat analysis of 5-year overall survival of patients listed for LT (n = 293) versus LR in patients potentially eligible for LT (n = 80); (b) Intention-to-treat analysis of 5-year disease-free survival of patients listed for LT (n = 293) versus LR in patients potentially eligible for LT (n = 80).

by multiorgan failure, 4 from multiorgan failure, 1 from sepsis and 1 from liver failure. The intra-operative number of transfused units of packed red blood cells did not differ (2774 ± 2838 vs. 3953 ± 3544 cc in primary vs. salvage LT, respectively) (p = NS).

The mean cold ischemia time (439 ± 106 vs. 425 ± 135 min., p = NS) and the incidence of postoperative complications were similar in the primary and salvage LT groups, respectively (Table 4).

Salvage transplantation versus primary LT

Twelve patients (75%) who underwent salvage LT had underlying hepatitis C virus-related cirrhosis or coinfection with hepatitis B virus in 3 cases (19%) and only 1 (6%) patient with SLT had HBV-related cirrhosis. Three patients received treatment for HCC before liver resection: 2 had previous TACE and 1 had previous alcohol injection. All liver resections were done by a transabdominal approach in all 16 patients resected for HCC and subsequently transplanted by salvage procedure either for HCC recurrence

Table 3: Intention-to-treat analysis of all patients listed for LT and LR potentially transplantable patients

Variables	Listed patients for LT (n = 293)	LR potentially transplantable (n = 80)	p
Gender M/F	245 (84%)/48 (16%)	63 (79%)/17 (21%)	NS
Age	54 ± 7	59 ± 6	<0.001
Cirrhosis etiology			
Alcohol	21 (7%)	8 (10%)	
HCV+	172 (59%)	61 (76%)	0.04
HBV+	82 (28%)	9 (11%)	
HCV+/HBV+	12 (4%)	2 (3%)	
Others	6 (2%)	–	
Child A	23 (8%)	66 (82%)	<0.001
Child B	139 (47%)	14 (18%)	
Child C	131 (45%)	–	
MELD	16.8 ± 9.1	8.56 ± 1.31	<0.001
Patients awaiting LT	74 (25%)	–	
Patients who died on waiting list:	43 (15%)	–	
- For tumor progression	14 (5%)	–	
- For others reasons	29 (10%)	–	
Patients excluded from waiting list:	29 (10%)	–	
- For tumor progression	20 (7%)	–	
- For *de novo* tumor	6 (2%)	–	
- For other reasons	3 (1%)	–	
Patients treated	147 (50%)	80 (100%)	<0.001
Patients alive:			
- Without HCC recurrence after LT or LR	105 (36%)	27 (34%)	
- Awaiting LT	74 (25%)	–	
- With HCC recurrence after LT or LR	2 (0.6%)	20 (25%)	
- With *de novo* tumor that excluded LT	1 (0.3%)		
- With tumor progression that excluded LT	7 (2.1%)		
Total patients alive	189 (64%)	47 (59%)	NS

LT = liver transplantation; LR = liver resection; MELD = model for end-stage disease; HCC = hepatocellular carcinoma.

Table 4: Postoperative complications in the primary and salvage LT groups

Variables	Primary LT (n = 147)	Salvage LT (n = 16)	p
Biliary complications	38 (26%)	5 (31%)	NS
Vascular complications	13 (9%)	1 (6%)	NS
Immunological complications	20 (14%)	3 (19%)	NS
Infections	31 (21%)	3 (19%)	NS
Neurological complications	12 (8%)	1 (6%)	NS
Primary graft nonfunction	5 (3%)	–	NS
Retransplantation	12 (8%)	–	NS
Total complications	131/147	13/16	NS
Total complicated patients	116/147 (79%)	10/16 (62%)	NS

LT = liver transplantation.

(n = 10/16) or for liver decompensation after LR (n = 6/16). Hepatectomy was limited to fewer than three segments in 4/16 patients (25%) and 1/16 patient (6%) underwent a right hepatectomy and in the remaining 11/16 patients (69%) a nonanatomical liver resection was performed.

There were no differences between the primary and salvage transplantation groups in age, gender or severity of the underlying cirrhosis. As regards the etiology of cirrhosis, HCV-related cirrhosis was more frequent in the salvage LT group, while HBV-related cirrhosis and alcohol cirrhosis were prevalent in the primary LT group (Table 5).

Table 5: Patients and tumor characteristics in the primary and salvage LT groups

Variables	Primary LT (n = 147)	Salvage LT (n = 16)	p
Gender M/F	126 (86%)/ 21(14%)	13 (81%)/ 3 (19%)	NS
Recipient age	55 ± 7	54 ± 8	NS
Cirrhosis etiology			
Alcohol	21 (14%)	–	
HCV+	79 (54%)	12 (75%)	
HBV+	43 (29%)	1 (6%)	
HCV+/HBV+	4 (3%)	3 (19%)	0.007
Child A	6 (4%)	6 (37%)	
Child B	53 (36%)	3 (19%)	NS
Child C	88 (60%)	7 (44%)	
MELD	17.8 ± 10.7	17.6 ± 6.0	NS
Tumor characteristics before LT			
Max size (mm.)	12.7 ± 13.4	24.3 ± 7.1	NS
>30 mm	13 (9%)	1 (6%)	NS
Mean no of nodules	1.7 ± 1.2	2.8 ± 1.5	NS
AFP (ng/mL)	42 ± 97	23 ± 42	NS
Pre-LT treatments			
TACE	55 (37%)	7 (44%)	
Alcohol injection	3 (2%)	1 (6%)	
RFA	10 (7%)	2 (12%)	
All treatments	68 (46%)	10 (62%)	NS

AFP = alpha-feto protein; RFA = radio-frequency ablation; TACE = trans-arterial chemoembolisation; LT = liver transplantation; MELD = model for end-stage disease.

Tumor characteristics preceding LT were similar in terms of maximum tumor size and of the number of nodules (Table 5). The mean time on the waiting list was similar (5.5 ± 6.4 vs. 8.2 ± 6.5 months) in the primary and salvage LT groups, respectively. During the waiting time for LT, 10 (62%) patients in the salvage LT group, all transplanted for HCC recurrence, were treated by preoperative nonsurgical treatment: TACE, RFA and PEI versus 46% treated in the same way in the primary LT group (p = NS) (Table 5).

The median time from resection to transplantation was 2.1 years (0.8–5.5) in the subgroup of 10 patients with HCC recurrence. For this reason, every patient with HCC recurrence (n = 10/16) that awaited a salvage procedure had pretransplant therapy (RFA, or TACE, or PEI) to avoid dropout from the waiting list due to tumor progression.

The median time from resection to transplantation, in the subgroup of 6 patients transplanted for hepatic decompensation was 1.1 years (0.6–2.6).

The mean follow-up time was similar between the primary and salvage LT groups (36 ± 32 vs. 26.2 ± 26.3 months, p = NS).

Tumor recurrence appeared in 3 out of 16 patients (19%) who underwent salvage LT versus 13 out of 147 patients (9%) with primary LT (p = NS).

Posttransplant overall 5-year survival was 62% versus 73% in the salvage and primary LT groups, respectively (p = NS) (Figure 3A). Five-year disease-free survival was 48% versus 71%.in the salvage and primary LT groups, respectively (p = NS) (Figure 3B).

Discussion

As a consequence of the high rate of HCC recurrence in patients with HCC submitted to LR versus patients submitted to LT, this study shows that LT after liver resection is safe and feasible with minimal operative mortality, similar operative morbidity, no increased risk of recurrence and similar long-term outcomes compared to primary LT.

LT is theoretically the treatment of choice for HCC on cirrhosis because it is the only procedure dealing both with the tumor and the underlying chronic liver disease, providing the most radical oncological resection of malignant or premalignant lesions as well as the best treatment for complications of cirrhosis. As a result, HCC recurrence is less frequent in the transplant group irrespective of liver function status (Child B-C vs. Child A): in particular, in the LT group only 4% of patients were Child A.

The superiority of LT over liver resection has been shown in terms of reduced incidence of recurrence and improved survival (24–26). However, recent LR studies suggest

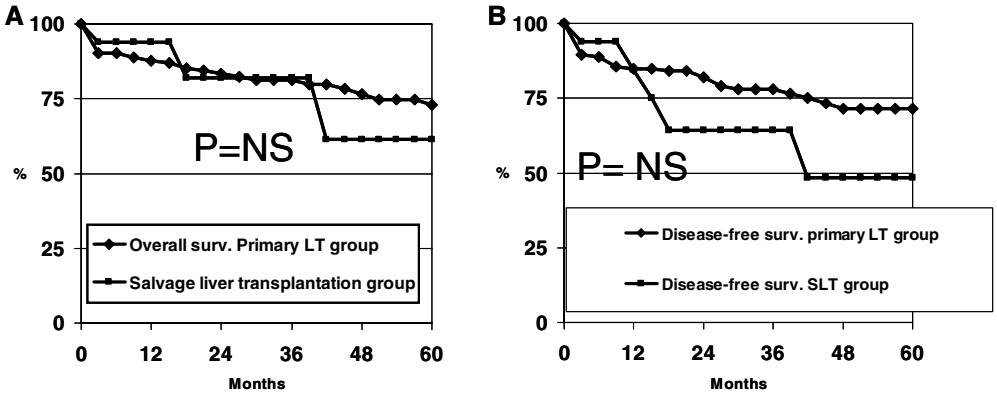

Figure 3: (A) Overall patient survival after primary (n = 147) versus salvage LT (n = 16); (B) disease-free patient survival after primary (n = 147) versus salvage LT (n = 16).

equivalent results to LT (27–29) and the clinical shortage of liver donors has limited the use of LT as a realistic option for all patients with HCC (30–32). Liver resection has therefore been considered as a reasonable first-line treatment for patients with small HCC and preserved liver function, with the perspective of LT as a salvage procedure in the event of recurrence (15,29,30,33).

Liver resection for Child A patients with a single nodule of HCC is now associated with a very low postoperative mortality (6,34) and a 5-year overall survival rate of up to 70% (7,9,35,36); the 3-year disease-free survival is 50% in most series (35,36), and the 5-year disease-free survival is up to 28% (7,9).

The minimal hospital readmissions rate of 7.5% in the LR group versus 15.5% in the LT group, found in our study population, shows that LR can be considered a good therapeutical option in Child A patients with HCC on cirrhosis without an increased risk in terms of reduced functional status.

Time of death was 37 months ± 32 months in the LR group versus 18 ± 23 months in the LT group, $p = 0.007$. On the basis of these data, liver resection determined a higher death rate with respect to liver transplantation (42% vs. 20%, $p < 0.0001$) mainly due to HCC recurrence and secondarily for liver decompensation, but time of death was later compared to the transplant group and, in consideration of the shortage of liver donors, this makes it possible to adopt the strategy of liver resection as the first-line treatment of HCC and liver transplantation secondarily in the event of HCC recurrence or liver decompensation. Furthermore, the similar 5-year overall survival of the two different surgical approaches (66% in the LR group vs. 58% in the LT group), which emerged from the intention-to-treat analysis between LR transplantable patients and patients listed for transplantation, reinforced the strategy of salvage procedure. In fact, by analyzing patients listed for transplantation it emerged that only 50% were actually transplanted while in 15% of cases the patients died on the waiting list and in 10% of cases, patients dropped out from the waiting list due to tumor progression (7%) or due to appearance of a *de novo* tumor (2%) or due to other reasons (1%). As a result, following the intention-to-treat analysis principle, 5-year disease-free survival is higher in patients listed for LT than LR patients (54% vs. 41%, respectively), but not statistically significant. This result can be interpreted by the fact that 82% of patients submitted to LR were Child A with an average MELD of 8.56 ± 1.31 and a lower number of nodules (1.1 vs. 1.7) compared to LT patients; if listed for transplantation first, such patients could have led to a high dropout from the waiting list due to the low Child class and MELD score and the subsequent tumor progression.

Majno et al. (19) found that the best outcome of resection was derived from the length of the waiting time for OLT. If the waiting time was less than 6 months, LT had a better predicted outcome than LR. In our study, the waiting times were longer than 6 months; in particular the mean time on the waiting list was 5.5 ± 6.4 months and this fact added value to the strategy of liver resection first for small HCCs on cirrhosis and salvage transplantation subsequently in the event of HCC recurrence or liver decompensation.

In our study we noted that 34% of potentially transplantable resected patients survived without recurrence for 5 years without the need for LT. Furthermore, among the 39 LR patients that developed HCC recurrence, 27 (69%) were within Milan criteria, 10 (37%) of these were submitted to salvage transplantation and 9 out of the 17 (53%) remaining patients are alive at the time of writing and theoretically suitable for many options of cure (salvage transplantation, liver re-resection, TACE or RFA) considering that the recurrence was in every case limited to the liver.

The refinement of radiological technique and strict follow-up programs have made it possible to detect HCC recurrence early, but considering time to recurrence in our study population (23 months ± 21 months in LR group vs.

15 ± 15 months in LT group, p = NS) and time to recurrence of 90% of the LR patients (57 months), the result probably suggests that the failure rate of our screening program is after the first 6 months following surgery where it could be better to perform abdominal ultrasonography on a 3-month basis for 5 years after surgery instead of every 6 months and also a chest-abdominal CT scan once a year.

In patients with HCC recurrence, secondary LT carried the same risk as primary LT, with a similar outcome. The 5-year disease-free survival in secondary LT was 48%. The major drawback in this approach was that only 26% of LR patients received LT in the event of tumor recurrence.

Cha et al. (37) calculated that the transplantation rate after HCC recurrence was as high as 87%, but in reality only 1 out of 16 patients with transplantable recurrence (6%) underwent salvage transplantation.

In the first reported series of 20 patients who underwent salvage procedure in clinical practice, by Adam et al. (38), the transplantation rate after tumor recurrence was 25% and after hepatic decompensation it was 3%. In the report by Paul-Brousse (38), the high recurrence rate and poor outcome after salvage LT was primarily due to a high operative mortality and intra-operative bleeding. These technical problems were probably the main drawbacks.

In fact, Belghiti et al. (33) reported 18 cases of salvage LT without increasing the 30-day mortality, the intra-operative number of transfused blood units, the morbidity or the incidence of HCC recurrence, or affecting long-term overall survival compared with primary LT. No information was available about the transplantation rate for HCC recurrence after LR.

Considering that the median time in our series between primary LR and secondary LT for HCC recurrence was 2.1 years, the salvage approach is a strategy that allows time to assess the biological behavior before entering the waiting list for LT without affecting the availability of cadaveric organs for other patients who are only put on the waiting list for severe end-stage liver disease.

Owing to the low real applicability of the salvage procedure (20%), in particular due to recipient age at the time of HCC recurrence and the dropout due to spread of the HCC while on the waiting list, how to select patients, previously submitted to LR, for salvage procedure is a matter of debate. Sala et al. (39) performed a prospective study on 16 patients offering LT immediately only to high pathological risk patients (n = 8) that had undergone LR with microvascular invasion, satellite nodules or additional nodules on the operative specimen without waiting for evidence of HCC recurrence.

On the other hand, in a retrospective study, Margarit et al. (40) stressed the concept of waiting for HCC recurrence, with a careful follow-up and offering LT only to patients with early HCC in the liver and excluding those with extrahepatic recurrence.

In our experience, we consider LT as a salvage procedure, only for patients that have undergone LR and have developed HCC liver recurrence. Analyzing our data retrospectively, we did not find any pathological risk factor related to a higher rate of recurrence, probably due to homogeneous biological characteristics of the HCCs considered in the analysis.

The adoption of the modified MELD score as a selection criterion for allocating cadaveric organs for patients on the waiting list for LT, as in our recent local policy, has kept the proportion of patients transplanted for HCC similar to non-HCC patients, without affecting the dropout rate from the waiting list of both groups of patients (22).

In another study considering a large cohort of patients resected for HCC on cirrhosis, we reported that the operative risk and long-term outcome can be satisfactory in patients with a MELD score less than 11 (41). In particular, in this study, as shown in Table 2, the average MELD score of 80 LR transplantable patients included in our study population was 8.56 ± 1.31 (6–11) and the long-term outcome of these patients is comparable to the LT group. Similar results have been reported by the Mayo Clinic group (42).

In conclusion, given the organ shortage, we believe that liver resection is an acceptable treatment with similar overall survival at 5 years, without an increase in perioperative complications to primary OLT but with an increased risk of recurrence in patients with small HCC and well-compensated cirrhosis, with salvage LT offered at the time of HCC recurrence or liver decompensation, as a safe and effective approach.

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